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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,695	11/21/2006	Toshihiro Tanaka	P29373	4545

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GREENBLUM & BERNSTEIN, P.L.C.
1950 ROLAND CLARKE PLACE
RESTON, VA 20191

EXAMINER
KAPUSHOC, STEPHEN THOMAS

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
07/23/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gbpatent@gbpatent.com
pto@gbpatent.com

Office Action Summary	Application No.	Applicant(s)	
	10/568,695	TANAKA ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-13* is/are pending in the application.

4a) Of the above claim(s) *5-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 4-13 are pending.

Claims 5-13 remain withdrawn from examination as detailed in the Office Action of 01/26/2009.

Claims 1 and 4 are examined on the merits.

This Office Action is in reply to Applicants' correspondence of 05/22/2009.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Claim Rejections - 35 USC § 101

1. The rejection of claims under 35 USC 101 as drawn to non-statutory subject matter, as set forth on pages 3-6 of the Office Action of 01/26/2009, is **WITHDRAWN** in light of the amendments to the claims.

Withdrawn Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

2. The rejection of claims under 35 USC 112 2nd ¶ as indefinite, as set forth on pages 6-7 of the Office Action of 01/26/2009, is **WITHDRAWN** in light of the amendments to the claims.

Withdrawn Claim Rejections - 35 USC § 112 1st¶ - Written Description

3. The rejection of claims under 35 USC 112 1st ¶ for lack of adequate written description, as set forth on pages 7-10 of the Office Action of 01/26/2009, is **WITHDRAWN** in light of the amendments to the claims.

Claim Rejections - 35 USC § 112 1st ¶ - Enablement
Maintained in part as necessitated by amendment

4. Claims 1 and 4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

The instant claims are drawn to methods for determining an increased risk of arteriosclerotic diseases, and specifically myocardial infarction, in humans.

The claims encompass any arteriosclerotic diseases.

The claims broadly recite detecting the presence or absence of a C at position 3279 of SEQ ID NO: 1, and thus the claimed methods do not require the detection of the recited nucleotide content.

The claims thus require knowledge of a correlative association between the a C at position 3279 of SEQ ID NO: 1 and an increased risk of arteriosclerotic diseases, and specifically myocardial infarction.

Direction provided by the specification and working example

The specification provides an example of the identification of a polymorphism in the human galectin-2 gene, where the polymorphic content is either a C or a T at position 3279 of SEQ ID NO: 1 (p.6-7).

The specification teaches (p.16; p.20-21), the analysis of the polymorphisms in case and control populations to study the association of the SNP content with the presence of myocardial infarction (MI). The specification asserts that the presence of the TT genotype at the position in both alleles of the galectin-2 gene is indicative of a decreased risk of MI (p.20).

The specification does not provide any examples of the analysis of any other arteriosclerotic diseases other than MI. There is no validation analysis of any additional population other than the subjects as presented in Table 1 on page 21 of the specification.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art with regard to the detection of any particular nucleotide sequence is high, the unpredictability with regard to the association of any particular sequence with a particular phenotype, or the identification of any nucleotide sequence has having a particular functionality, is even higher. The unpredictability is demonstrated by the prior art and the post-filing art.

Because the nature of the claimed methods requires knowledge of a robust and reliable association between nucleotide content and disease risk, it is relevant to point out the unpredictable nature of any mutation association study. As evidence of the unpredictability of gene association studies, Lucentini (2004) teaches that it is strikingly

common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph). Additionally, Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

The unpredictability as generally described by Lucentini and by Hegele, as cited above, is particularly relevant considering the teachings of the post-filing art. For example, the post filing-art teaches the analysis of the same SNP in the galectin-2 gene and a lack of association with MI. Mangino et al (2007) teach that the SNP rs7291467 (the same SNP of the instant application) is not associated with MI in a Caucasian population (p.114 left col.). Similarly, Sedlacek et al (2007) teaches (p.1000, Table 3) that there is no significant association between the same SNP and MI in two German

populations. Finally, Kimura et al teaches that there was no association of the SNP with MI in a Japanese population or a Korean population (p.267, left col.; Table 3). It is thus unpredictable as to weather or not the asserted association of the instant specification would in fact reliably or robustly be reproduced in any other different population.

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the claimed invention. Such experimentation would include large case:control studies to establish whether or not the asserted associations are reliable and robust in any subject population of interest. Such experimentation would be extensive. Even if one were to carry out such experimentation, there is no assurance that a reliable and consistent association of genetic content, consonant with the breadth of the claims, with any arteriosclerotic disease or even MI would be identified.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement. Applicants' arguments (p.7-15 of the Remarks) have been fully and

carefully considered but are not found to be persuasive to withdrawn the rejection. Initially it is noted that, in light of the amendments to the claims, the portions of the rejection as set forth in the previous Office Action regarding the claims as they encompass any alteration in the galectin-2 gene and the analysis of non-human subjects have been withdrawn from the instant rejection.

Applicants have argued (p.9-10 of Remarks) that The PROCARDIS Consortium article of 2004 indicates a role LTA in coronary artery disease, and that the required galectin-2 mutation affects LTA behavior, and thus it can be concluded that the required C/T at position 3279 can determine disease risk. The argument is not persuasive. At issue in the rejection of the instantly claimed methods is not whether galectin-2 and LTA participate is some mutual pathway related to coronary artery disease, but whether or not the skilled artisan can reliably discern the risk of arteriosclerosis of any human subject by detection the presence or absence of a particular nucleotide content in SEQ ID NO: 1.

The Examiner has cited the post filing art of Mangino et al, Sedlacek et al, and Kimura et al as evidence that in several separate populations the analysis of the same polymorphism as recited in the instant claims shows a lack of association with myocardial infarction. Applicants have argued (p.12 of Remarks) that the teachings of Mangino et al and Sedlacek et al should be discounted because those studies addressed European and American subjects which are not uniform in population. The argument has been fully and carefully considered but is not persuasive to withdraw the rejection. The claims require that the skilled artisan can reliably discern the risk of

arteriosclerosis of any human subject by detection of nucleotide content. The Examiner maintains that if the method as claimed is in fact enabled, the method should be applicable to any subject population. Applicants argue (p.13-14 of Remarks) that Kimura et al should be discounted as the reference concedes some weaknesses in their study. In this regard the Examiner points out that the USPTO does not have at its disposal clinical or experimental laboratory services to specifically test the required associations of claimed diagnostic methods, and must rely on the data provided in the post-filing art. And while Applicants point out that some population analyses that are possible to perform were not performed by Kimura et al, the Examiner maintains and reiterates that if the method as claimed is in fact enabled, the method should be applicable to any subject population. In the instant case, the preponderance of evidence provided by the post filing art of Mangino et al, Sedlacek et al, and Kimura et al (and also Koch et al (2007) (see Tables 2 and 3)) supports the Examiner's conclusion that in fact there is not a reliable and robust relationship between the required nucleotide content and risk of arteriosclerotic disease.

The rejection as set forth is **MAINTAINED.**

Conclusion

5. No claim is allowed.

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action

is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Art Unit 1634